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(19) Europäisches Patentamt
European Patent Office
Offic eur péen des brev ts

(11) Publication number: **0 430 474 B1**

(12) # EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification: **08.02.95**

(51) Int. Cl.[6]: **A61K 9/70**, A61K 9/22

(21) Application number: **90312249.7**

(22) Date of filing: **08.11.90**

The file contains technical information submitted after the application was filed and not included in this specification

(54) **Sustained release compositions for treating periodontal disease.**

(30) Priority: **17.11.89 US 439066**
24.08.90 US 573604

(43) Date of publication of application:
05.06.91 Bulletin 91/23

(45) Publication of the grant of the patent:
08.02.95 Bulletin 95/06

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IT LI LU NL SE

(56) References cited:
EP-A- 0 025 698
EP-A- 0 244 118
US-A- 3 608 057
US-A- 4 048 256
US-A- 4 568 536

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EP 0 430 474 B1

Description

This invention relates to compositions/devices for treating diseases of the oral cavity which compositions/devices are placed in or around the periodontal pocket.

Periodontal disease, for example, is a major cause of tooth loss in adults. Tooth loss from periodontal disease is a significant problem beginning at age 35, but even by age 15 it is estimated that about 4 out of 5 persons already have gingivitis and 4 out of 10 have periodontitis.

While good oral hygiene, as achieved by brushing the teeth with a cleansing dentifrice, may help reduce the incidence of periodontal disease, it does not necessarily prevent or eliminate its occurrence. This is because microorganisms contribute to both the initiation and progress of periodontal disease. Thus, in order to prevent or treat periodontal disease, these microorganisms must be suppressed by some means other than simple mechanical scrubbing. Towards this end, there has been a great deal of research aimed at developing therapeutic dentifrices, mouthwashes, and methods of treating periodontal disease which are effective in suppressing these microorganisms.

Recent developments in the art are directed toward delivering the therapeutic agent directly to the periodontal pocket, in some cases in a controlled release formulation. Gordon et al. have described the use of a drug-filled polymer hollow fiber. (J.M. Goodson et al., "Periodontal Therapy by Local Delivery of Tetracycline", J. Clin. Periodontal. 6, 83 (1979), J. Lindhe et al., "Local Tetracycline Delivery Using Hollow Fiber Devices in Periodontal Therapy", J. Clin. Periodontal. 6, 141 (1979) and R.L. Dunn et al., "Monolithic Fibers for Controlled Delivery of Tetracycline", in Proc. Ninth Int. Symposium on Controlled Release of Bioactive Materials, Ft. Lauderdale, FL, July (1982). This device is tied around a tooth and gently pressed below the margin of the gingiva so that it resides in the periodontal pocket, and is capable of delivering an effective dose of 2.5 micrograms of tetracycline per day per periodontal pocket for a prolonged period of a week or more. Similar results have been obtained by Coventry and Newman (J. Coventry and H. N. Newman, "Experimental Use of a Slow Release Device Employing Chlorhexidine Gluconate in Areas of Acute Periodontal Inflammation", J. Clin. Periodontal. 9, 129 (1982) and Addy et al. (M. Addy et al., "The Development and in vitro Evaluation of Acrylic Strips and Dialysis Tubing for Local Drug Delivery", J. Periodontal 53, 693 (1982) using acrylic strips 1mm or more long, impregnated with chlorhexidine, tetracycline or metronidazole, which were inserted into the periodontal pocket with tweezers. Such a strip, formed from ethylcellulose impregnated with metronidazole, is disclosed by Loesche in US-A-4,568,538 (February 1986). Another strip, employing a water soluble polymer of a particular elasticity and viscosity, is disclosed by Suzuki et al. in US-A-4,569,837.

In addition to the above approaches, the prior art also discloses using putty-like compositions containing an antimicrobial for insertion into the periodontal pocket. A material disclosed as suitable is a copolymer of lactide and glycolide. See US-A-4,650,665, March 17, 1987 to Kronenthal et al..

The present inventor has discovered that lactide and glycolide copolymers have limited pliability and solubility in terms of processing.

It is therefore an object of the present invention to provide lactide/glycolide compositions/devices suitable for treating diseases of the oral cavity overcoming such problems.

It is a further object of the present invention to provide such compositions/devices using copolymers of lactide and glycolide and using propylene carbonate as a solvent/plasticizer.

All percentages and ratios used in here are by weight unless otherwise indicated.

All measurements are made at 25 °C unless otherwise indicated.

According to the present invention there is provided a liquid, semi-solid or solid composition for insertion into or around the periodontal pocket of a person or lower animal suffering from diseases of the oral cavity comprising a copolymer of lactide and glycolide in a concentration from 10% to 90% wherein the molar percentage of lactide units is from 15% to 85%, a drug active selected from antiinflammatory agents, antimicrobials, antibiotics, peroxides, anesthetic agents and vitamins in a concentration from 1% to 75% and propylene carbonate in a concentration from .1% to 70%, the ratio of the components being such that the drug active is released at a rate to provide steady state number average concentrations of from 10 micrograms to 2000 micrograms per milliliter of the gingival crevicular fluid of a treated periodontal pocket.

The essential as well as optional components of the compositions/devices of this invention are described below.

Lactide/Glycolide Copolymers

The copolymers of the present invention contain mixtures of lactide and glycolide monomers. Lactide monomeric species preferably comprise 15% to 85%, most preferably from 35% to 65%, of the polymers

while glycolide monomers comprise from 15% to 85% of the polymer, preferably from 35% to 65% on a molar basis. The molecular weight of the copolymer lies in the range of from 1000 to 120,000 (number average). These polymers are described in detail in US-A-4,443,430, April 17, 1984, to Mattei.

The polymer generally comprises from 10% to 90%, preferably from 20% to 70% of the compositions/devices of the present inv ntion. Less polymer is necessary as the amount of lactide goes up.

Propylene Carbonate

The second essential component of the present invention is propylene carbonate. This is a material of commerce and is used in the present compositions/devices at a level of from 0.1% to 70%, preferably from 1% to 70%, most preferably from 3% to 50%. The higher levels of propylene carbonate, are used when it is desired that the compositions be in gel or liquid form rather than in solid form.

Drug Active

The drugs useful for use in the present compositions/devices are varied and many and include any agent which provides treatment or prevention management of diseases of the oral cavity. Some therapeutic agents which are amenable to delivery by this means and are potentially of value for periodontal therapy, include (but are not limited to) antibacterial agents such as iodine, sulfonamides, mercurials, bisbiguanides, or phenolics; antibiotics such as tetracycline, neomycin, kanamycin, metronidazole, or clindamycin; antiinflammatory agents such as aspirin, naproxen, ibuprofen, flurbiprofen, indomethacin, eugenol, or hydrocortisone; immune-suppressive or stimulatory agents such as methotrexate or levamasole; dentinal desensitizing agents such as strontium chloride or sodium fluoride; odor masking agents such as peppermint oil or chlorphyll; immune reagents such as immunoglobulin or antigens; local anesthetic agents such as lidocaine or benzocaine; nutritional agents such as amino acids, essential fats, and vitamin C; antioxidants such as alphatocopherol and butylated hydroxy toluene; llpopolysaccharide complexing agents such as polymyxin; or peroxides such as urea peroxide. It is recognized that in certain forms of therapy, combinations of these agents in the same delivery system may be useful in order to obtain an optimal effect. Thus, for example, an antibacterial and an antiinflammatory agent may be combined in a single delivery system to provide combined effectiveness.

The drug active is used at a level of from 1% to 75%, preferably from 5% to 75%, most preferably from 10% to 50% of the compositions/devices. The compositions/devices, are designed to release drug to provide steady state number average concentrations of from 10μg to 2000μg, preferably from 50μg to 1500μg, most preferably from 100μg to 1000μg per milliliter of the gingival crevicular fluid of a treated periodontal pocket. The steady state release rates can be altered by varying component ratios of the compositions. The steady state conditions are preferably used since initial bursts are accounted for as well as delays in release. For example, in the case of a ten (10) day therapy, steady state is generally reached in about one to two days.

Optional Components

In addition to the drug active, the compositions/devices of the present invention may include a variety of optional components. Such components include, but are not limited to, surfactants, viscosity controlling agents, complexing agents, antioxidants, other polymers such as carboxymethyl cellulose, gums such as guar gum, waxes/oils such as castor wax, castor oil, glycerol, dibutyl phthalate and di(2-ethylhexyl) phthalate as well as many others. If used, these optional components comprise from about 0.1% to about 20%, preferably from about 0.5% to about 5% of the total composition/device.

METHOD OF MANUFACTURE

Method of manufacturing the compositions/devices of this invention are disclosed in the Examples.

EXAMPLE I

The following is an exemplary composition/device of the present invention.

	Wt. %
Tetracycline hydrochloride	50
Poly(lactyl-co-glycolide)/50:50 copolymer	45.4
Propylene Carbonate	4.6

The above composition can be prepared in a number of different ways. One way is as follows: Polymer is charged into a 110°C, electrically heated mixer, equipped with high shear Sigma type rotor blades. Propylene carbonate is added and mixed into the polymer. The drug is added and mixed until uniform. The drug polymer blend is removed for further processing into desired size and shape devices.

The compositions/devices of the invention of this application are inserted into the periodontal pocket or gingival region, and may be administered in the form of a particle, film or sheet. The size, shape, and thickness can be changed according to the condition of the disease to be treated and they are not particularly critical. Ordinarily, the size, shape, and thickness are changed according to the size of the periodontal pocket of the patient or the condition of the gingiva. The devices may be for example of a size such that the thickness is in the range of 0.01 to 2mm, preferably from 0.1 to 1mm; the width in the range of 0.1 to 5mm, preferably from 0.1 to 4mm; and the length in the range of from 1 to 15mm, preferably from 3 to 10mm.

If in the above example, the propylene carbonate level is increased to about 30%, the composition is in the form of a gel which may be put into the periodontal pocket.

EXAMPLE II

	Wt. %
Tetracycline hydrochloride	50
Poly(lactyl-co-glycolide)/50:50 copolymer	45.4
Propylene Carbonate	4.6

The composition of the Example II was tested in human volunteers having periodontal disease. For the purpose of this test, periodontally involved sites were selected in five periodontitus human volunteers. Strips of the composition of Example II, having about 0.75mm thickness and about 0.9mm width were cut in length to fit individual pocket depth in length, and inserted into the cavities. Samples of gingival crevicular fluid from each of the treated sites were collected daily for at least 10 days using Periopaper®. Volume of the collected fluid was determined using Periotron® instrument, model number 6000. All the samples were analyzed for the drug content using microbiological bioassay procedure. Results of this test are shown in the following:

Micrograms Drug in Gingival Crevicular Fluid										
Subject ID	Day#									
RT	1619	475	3366	710	463	613	558	2734	947	1104
PA	1413	504	162	n/a	742	1559	1780	385	1780	160
FL	24	34	56	76	180	2654	794	162	860	63
GP	70	87	578	1262	431	n/a	43	831	1471	n/a
CB	1516	1329	n/a	n/a	1625	905	774	1777	3466	1492

The devices were removed by flushing from the treated sites on the 12th day following their insertion.

The above results show that the drug is released in a sustained manner for over a week, which is adequate for the antibiotic treatment of periodontally involved sites.

While solid phase devices of the compositions illustrated above are very useful and convenient for most treatments, there may also be need for fluid compositions that can be inserted via syringe, and either a needle or catheter into the periodontal cavities. Examples of such instances include difficult to reach areas where the periodontal cavities are irregular, narrow and very deep or those involving furcations. For this reason, fluid gel or paste compositions are developed based on the above mentioned principles of the compounding the poly(lactyl-co-glycolide) polymers as illustrated in the following:

Laboratory studies have been conducted for gel compositions using propylene carbonate as carrier solvent with or without propylene and/or polyethylene glycol for poly(lactyl-co-glycolide) polymer. Representative examples of such sustained release compositions are as follows:

EXAMPLE III

	Wt. %
Tetracycline hydrochloride	27
Poly(lactyl-co-glycolide)	24
Propylene carbonate	44

EXAMPLE IV

	Wt. %
Tetracycline Base	27
Poly(lactyl-co-glycolide)	24
Propylene carbonate	40
Polyethylene glycol 400	9

EXAMPLE V

	Wt. %
Chlorhexidine diacetate	40
Poly(lactyl-co-glycolide)/50:50 copolymer	20
Propylene carbonate	40

Compositions corresponding to the above Examples can be prepared by a variety of pharmaceutical or cosmetic procedures. For example, composition of Example II can be prepared by first dissolving the copolymer into the propylene carbonate using a propeller mixer. Micronized drug is slowly added and mixed into the polymeric solution to a uniform consistency. Such compositions are gel like fluids which can be inserted into the diseased periodontal cavities via syringe.

Surprising feature of such fluid or paste like compositions is their transformation into near solid phase in the presence of aqueous fluid such as water, aqueous buffers or crevicular fluid. For example, when a sample of such a gel is placed into a tube containing water or human serum, the composition becomes nearly solid in the receptor phase. This is believed to be due to insolubility of the poly(lactyl-co-glycolide) copolymers in water, and related aqueous solvents. Thus, even though such fluid compositions can be used advantageously when desired from syringe like apparatus, they still offer uncompromised advantages of solid devices at the treatment sites. Further, since such polymeric materials do undergo slow degradation via hydrolysis, the drug continues to release in a sustained manner from such compositions.

For the purpose of experim ntal evaluation, stainless st el wire loops were fabricated to provide 0.5 cm. internal diameter. Loops were filled with test compositions, and the test samples were lowered into vials filled with pH 7.4 phosphate buffers. In contact with the fluid receptor a g l of Example III transformed into near solid phase in about a minute. Initially, the drug is released to provide a burst, during the phase

transition stage providing a loading dose. Once the gel transforms into solid phase, drug release rate slows down to a more controlled rate. This dual phase release pattern is, in fact, highly desirable in practice for the treatment of microbial infection. The receptor fluids of each of the test vials were exchanged with same volume of the fluid every day for at least seven days for the purpose of this experiment.

Results of this experiment showed that the drug is released from such gel compositions in a sustained manner.

Quantity of the drug released from the respective compositions can be varied by selecting factors such as solubility of drug by proper selection of its salt or ester, drug loading in the composition, molecular weight of the copolymer or adding other polymer. The composition of the Example II, containing tetracycline hydrochloride salt releases drug at a faster rate compared to the drug released from the composition of the Example III. This is due to the fact that the hydrochloride salt of tetracycline is about six times more soluble than the tetracycline base.

This series of experiments demonstrate that sustained release fluid gel or paste compositions of poly-(lactyl-co-glycolide) can be formulated using propylene carbonate pharmaceutically acceptable solvent of this invention without using any objectionable organic solvents such as acetone or methylene chloride for delivery of the drugs into the body cavities.

Claims

1. A liquid, semi-solid or solid composition for insertion into or around the periodontal pocket of a person or lower animal suffering from diseases of the oral cavity comprising a copolymer of lactide and glycolide in a concentration from 10% to 90% wherein the molar percentage of lactide units is from 15% to 85%, a drug active selected from antiinflammatory agents, antimicrobials, antibiotics, peroxides, anesthetic agents and vitamins in a concentration from 1% to 75% and propylene carbonate in a concentration from .1% to 70%, the ratio of the components being such that the drug active is released at a rate to provide steady state number average concentrations of from 10 micrograms to 2000 micrograms per milliliter of the gingival crevicular fluid of a treated periodontal pocket.

2. A composition according to Claim 1 wherein the number average molecular weight of the copolymer is from 1000 to 120,000.

3. A composition according to Claim 2 wherein the concentration of the drug active is from 10% to 50% and the active is selected from the tetracycline group of antibiotics.

4. A composition according to Claim 3 wherein the composition is formed into a shape having a width of from 0.1mm to 5mm, a thickness of from 0.01mm to 2mm and a length of from 1mm to 15mm.

Patentansprüche

1. Flüssige, halbfeste oder feste Zusammensetzung zum Einführen in die Zahnfleischtasche oder zum Anbringen um dieselbe herum, bei einer Person oder einem niedrigeren Tier, welche bzw. welches an Erkrankunger der Mundhöhle leidet, welche Zusammensetzung ein Copolymer aus Lactid und Glycolid in einer Konzentration von 10 % bis 90 %, wobei der Molprozentsatz der Lactideinheiten 15 % bis 85 % ausmacht, einen Arzneimittel-Wirkstoff, der aus entzündungshemmenden Mitteln, antimikrobiellen Mitteln, Antibiotika, Peroxiden, anästhetischen Mitteln und Vitamiren ausgewählt ist, in einer Konzentration von 1 % bis 75 %, und Propylencarbonat in einer Konzentration von 0,1 % bis 70 % umfaßt, wobei das Verhältnis der Komponenten ein solches ist, daß der Arzneimittel-Wirkstoff mit einer solchen Geschwindigkeit freigesetzt wird, daß dadurch im Fließgleichgewichtszustand zahlenmäßige mittlere Konzentrationen von 10 µg/ml bis 2000 µg/ml der Zahnfleischtaschenflüssigkeit einer behandelten Zahnfleischtasche geschaffen werden.

2. Zusammensetzung nach Anspruch 1, wobei das zahlenmäßige mittlere Molekulargewicht des Copolymers 1000 bis 120.000 beträgt.

3. Zusammensetzung nach Anspruch 2, wobei die Konzentration des Arzneimittel-Wirkstoffes 10 % bis 50 % ausmacht und wobei der Wirkstoff aus der Tetracyclingruppe von Antibiotika ausgewählt ist.

4. Zusammensetzung nach Anspruch 3, wobei die Zusammensetzung zu einer Gestalt geformt wird, welche eine Breite von 0,1 mm bis 5 mm, eine Dicke von 0,01 mm bis 2 mm und eine Länge von 1 mm bis 15 mm aufweist.

Revendicati ns

1. Composition liquide, semi-solide ou solide à insérer dans ou autour de la poche parodontale d'une personne ou d'un animal inférieur souffrant de maladies de la cavité buccale, comprenant un copolymère de lactide et de glycolide, en concentration de 10% à 90%, dans lequel le pourcentage molaire des motifs lactide est de 15% à 85%, une substance active médicamenteuse choisie parmi les antiinflammatoires, les antimicrobiens, les antibiotiques, les peroxydes, les anesthésiques et les vitamines, en concentration de 1% à 75%, et du carbonate de propylène en concentration de 0,1% à 70%, le rapport des constituants étant tel que la substance active médicamenteuse est libérée à une vitesse fournissant des concentrations moyennes en nombre constantes, de 10 microgrammes à 2 000 microgrammes par millilitre du fluide alvéolaire gingival d'une poche parodontale traitée.

2. Composition selon la revendication 1, dans laquelle la masse moléculaire moyenne en nombre du copolymère est de 1 000 à 120 000.

3. Composition selon la revendication 2, dans laquelle la concentration de la substance active médicamenteuse est de 10% à 50% et la substance active est choisie dans le groupe d'antibiotiques tétracyclines.

4. Composition selon la revendication 3, dans laquelle la composition est mise sous une forme ayant une largeur de 0,1 mm à 5 mm, une épaisseur de 0,01 mm à 2 mm et une longueur de 1 mm à 15 mm.